1 456 550

PATENT SPECIFICATION

(11) 1 456 550

(21) Application No. 45131/74 (22) Filed 17 Oct. 1974
(31) Convention Application No. 7 337 344
(32) Filed 19 Oct. 1973 in
(33) France (FR)
(44) Complete Specification published 24 Nov. 1976
(51) INT CL² A61K 31/565
(52) Index at acceptance A5B 240 241 243 246 24Y

(19)

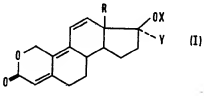
(54) ZOOTECHNICAL AND VETERINARY COMPOSITIONS

(71) We, ROUSSEL-UCLAF, A French Body Corporate, of 35 Boulevard des Invalides, Paris 7eme, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns zootechnical and veterinary compositions. In particular, it relates to zootechnical compositions which may be of use for increasing the bodyweight of livestock, and it relates to veterinary compositions which may be of use in the medical treatment of livestock.

The invention thus provides zootechnical compositions comprising:

a) an anabolising steroid of the general formula:



(I)

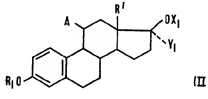
wherein:

R represents an alkyl radical containing from 1 to 4 carbon atoms;

X represents a hydrogen atom, a saturated or unsaturated hydrocarbyl radical containing from 1 to 6 carbon atoms one of which can be replaced by an oxygen atom, or the acyl residue of an organic carboxylic acid containing from 1 to 18 carbon atoms; and

Y represents a hydrogen atom or a saturated or unsaturated hydrocarbyl radical containing from 1 to 4 carbon atoms; and

b) an estrogenic steroid of the general formula:



(II)

wherein:

R_1 represents hydrogen, an alkyl radical having from 1 to 5 carbon atoms, or a *cyclo*alkyl radical having from 3 to 7 carbon atoms;

A represents hydrogen or a β-alkoxy radical in which the alkyl moiety contains from 1 to 4 carbon atoms;

R' represents an alkyl radical having from 1 to 4 carbon atoms;

X_1 represents hydrogen, an alkyl radical containing from 1 to 4 carbon atoms, or the acyl residue of carbonic acid or a carboxylic, aliphatic or alicyclic, organic acid having from 1 to 10 carbon atoms; and

Y_1 represents hydrogen, a methyl radical, an ethynyl radical, or a haloethynyl radical.

R preferably represents a methyl radical or especially, an ethyl radical.

X preferably represents: a hydrogen atom (especially); an alkyl radical containing from 1 to 4 carbon atoms (especially a methyl, ethyl, propyl, *iso*propyl, butyl or *iso*butyl radical); an alkyl radical containing from 2 to 4 carbon atoms; an alkoxyalkyl radical containing from 2 to 4 carbon atoms (especially a methoxymethyl radical); an unsaturated hydrocarbyl radical containing from 2 to 6 carbon atoms (especially a 2-methylallyl or 3-methyl-2-butenyl radical); the acyl residue of an alkanoic acid (such as formic, acetic, propionic, butyric, *iso*butyric or undecylic acid); the acyl residue of a *cyclo*alkylcarboxylic or *cyclo*alkylalkanoic acid (such as *cyclo*propyl; *cyclo*pentyl- or *cyclo*hexylcarboxylic acid, or *cyclo*propyl-, *cyclo*pentyl- or *cyclo*hexylacetic or -propionic acid); the acyl residue of benzoic acid; or the acyl residue of phenylacetic or phenylpropionic acid.

Y preferably represents a hydrogen atom or a methyl radical.

R_1 preferably represents a hydrogen atom or a methyl radical.

A preferably represents a hydrogen atom or a methoxy radical.

R' preferably represents a methyl or ethyl radical.

X_1 preferably represents: a hydrogen atom; the acyl residue of formic, acetic, propionic, butyric or *iso*butyric acid; the acyl residue or *cyclo*propyl-, *cyclo*pentyl- or *cyclo*hexylcarboxylic acid; the acyl residue of *cyclo*propyl-, *cyclo*pentyl-, or *cyclo*hexylacetic or -propionic acid; the acyl residue of benzoic acid; or the acyl residue of phenylacetic or phenylpropionic acid.

Y_1 preferably represents a hydrogen atom or a methyl radical.

A particularly preferred anabolising steroid I is 2-oxa-13-β-ethyl-17α-methyl-17β-hydroxy-gona-4,9,11-trien-3-one.

A particularly preferred estrogenic steroid II is estradiol.

The anabolising steroids I can be prepared according to the processes indicated in British Patents Nos. 1,146,868, 1,251,025, 1,251,026, 1,251,027 and 1,251,028, French Certificates of Addition Nos. 251 CAM, 256 CAM and 273 CAM and French Patent No. 2,092,780.

The estrogenic steroids II can be prepared according to French Patents Nos. 1,514,122, 1,540,942 and 1,476,509.

The zootechnical compositions of the invention may be of use for the promotion of weight gains in livestock animals such as cattle and pigs. The compositions may be administered in all the usual ways, but are in particular capable of being administered by deposition in the dermis of the animal.

One of the interesting features of the compositions of the invention lies in the fact that association of the two active principles (an anabolising steroid and an estrogenic steroid) entails only a minimal disturbance in livestock animals whilst nevertheless permitting both a more rapid gain in weight and also an improvement in the quality of the meat. In addition, the compositions are not liable to leave in the animal's organism hormone products the effect of which could be harmful to the consumer of the meat.

Finally, the simultaneous presence of the two active principles reinforces the favourable action on the growth of one and the other, so that the result of this is a substantially higher gain in weight.

The compositions of the invention display both zootechnical properties and veterinary properties. They exhibit, in particular, anabolising properties—especially protidic anabolising properties (as is made evident by the physiological test results given hereinafter)—and these properties may make the compositions suitable for use as veterinary medicaments to increase general organic resistance to attacks of all kinds, to control retarded growth, emaciation, and general organic disorders connected with a state of senescence, and also to control (as a side effect) infectious, parasitic and nutritional illnesses. Of course, before the compounds I and II may be used either in zootechnical or in veterinary compositions, they should preferably be associated with a suitable vehicle. The nature of the vehicle, considered of course, in relation to the route by which the composition is intended to be administered, is naturally chosen so as to exclude any possibility that the composition could be harmful rather than beneficial. The choice of a suitable mode of presentation, together with an appropriate vehicle, is believed to be within the competence of those accustomed to the preparation of zootechnical and veterinary formulations.

The compositions of this invention may, for example, be administered orally,

transcutaneously or by implantation, and, in respect of these modes, the vehicle is preferably:—

a) the ingestible excipient of a tablet, coated tablet, or pill; the ingestible container of a capsule or catchet; the ingestible pulverulent solid carrier of a powder; or the ingestible liquid medium of a syrup, solution, suspension or elixir;
b) a sterile injectable liquid solution or suspension medium; or
c) a soluble material, or a base material, capable of releasing the active ingredient to perform its pharmacological function, which excipient material when appropriately shaped forms an implant.

Whilst the modes of presentation just listed represent those most likely to be employed, they do not necessarily exhaust the possibilities.

The compounds of this invention may preferably be administered in the form of tablets: of injectable solutions or suspensions dispensed in single-dose ampoules or multi-dose phials; and implants.

Whilst the dosages of the active ingredient will, to a certain degree, depend upon the route by which the compositions are to be administered, upon the purpose for their use, and upon the animal concerned, nevertheless, by way of general indication it may be said that the useful dose for cattle, and more particularly for calves, is from 1 mg to 300 mg (preferably from 25 mg to 200 mg) of anabolising steroid I, and from 1 mg to 60 mg (preferably from 10 mg to 50 mg) of estrogenic steroid II. These doses are conveniently administered as a single, unit dose.

In view of their administration to cattle, the compositions can most preferably be deposited as an implant in the dermis, especially at the base of the ear.

They can, however, also be administered in the neck of the animal, or in the rump muscles, and while in general they can either be implanted or injected (in the form of a solution or suspension), implants have the advantage of being better resorbed.

The compositions can be prepared by conventional methods.

This invention also extends to a method for the zootechnical and/or veterinary treatment of livestock animals, in which process there is administered to the animal concerned a suitable dose of a composition as described and claimed herein.

The following formulation Example and Test Results are now given, though only by way of illustration, to shown details of the compositions of the invention.

Example: Zootechnical Composition

A compressed tablet implant was formulated from the following ingredients:

estradiol ..... 20 mg

2-oxa-13β-ethyl-17α-methyl-17β-hydroxy-gona-4,9,11-trien-3-one ..... 70 mg

excipient ..... q.s. for a compressed tablet.

Test Results: Action of the compositions upon cattle:

The test was carried out on 28 male calves of the "black and white" variety. The animals were divided into two batches of 14 calves:

1) a control batch; and
2) a batch of animals implanted with a compressed tablet according to the formulation Example given above.

The implants were introduced under the skin into the connective tissue situated at the base of the ear thirty-three days before slaughtering. All the animals received the same quantity.

The results are assembled in the Table below, in which:

$$\text{yield} = \frac{\text{Weight of the carcass}}{\text{Total weight of the animal}}, \text{ and}$$

$$\text{consumption index} = \frac{\text{Weight of food which the animal has received}}{\text{Total gain in weight}};$$

and in which the carcasses were classified according to the criteria:

conformation : rated from 1 to 3,

colour : rated from 1 to 3, and

fat condition : rated from 1 to 3.

In each case 1 is the best rating, and the Table shows how many carcasses received each rating for each criteria. All the weight figures are, of course, averages.

TABLE

	Controls	Implanted animals
Weight upon arrival (kg)	39.44	39.48
Weight before implantation (kg)	78.57	78.50
Gain in weight before treatment (kg)	39.13	39.01
Weight at slaughtering (kg)	148	157.71
Gain in weight (total period) (kg)	108.66	118.23
Daily gain in weight (kg)	0.906	0.985
Weight of the carcasses (kg)	92.71	99.28
Yield	62.62	62.93
Colour 1	5/14	6/14
Colour 2	9/14	8/14
Colour 3	0/14	0/14
Conformation 1	3/14	10/14
Conformation 2	5/14	2/14
Conformation 3	6/14	2/14
Fat Condition 1	12/14	14/14
Fat Condition 2	2/14	0/14
Fat Condition 3	0/14	0/14
Consumption index	1.69	1.57

From these results it is clear that the implanted animals have, with regard to the controls, a higher gain in weight and yield, a better colour, conformation and fat condition, and a lower consumption index.

Research into the histological modifications of the prostate in the calf

Immature male calves, separated into three groups, were used in this test:

1) a control group I (which did not receive any implants);

2) a control group II implanted with a compressed tablet of 20 mg estradoil only; and

3) a test group III implanted with a compressed tablet according to the formulation Example hereinabove.

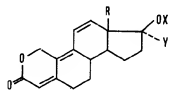
The implants were administered by sub-cutaneous route, and the animals were slaughtered 90 days later.

It was found that the animals treated with estradiol (group II) had pronounced prostate metaplasiae, whereas the animals treated with the inventive composition (group III) did not. Clearly, therefore, the hormonal effects of estradiol are thus nullified in the compositions of the invention.

WHAT WE CLAIM IS:—

1. A zootechnical and/or veterinary composition comprising:

a) an anabolising steroid of the general formula:



(I)

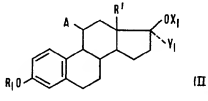
wherein:

R represents an alkyl radical containing from 1 to 4 carbon atoms;

X represents a hydrogen atom, a saturated or unsaturated hydrocarbyl radical containing from 1 to 6 carbon atoms one of which can be replaced by an oxygen atom, or the acyl residue of an organic carboxylic acid containing from 1 to 18 carbon atoms; and

Y represents a hydrogen atom or a saturated or unsaturated hydrocarbyl radical containing from 1 to 4 carbon atoms; and

b) an estrogenic steroid of the general formula:



(II)

wherein:

R_1 represents hydrogen, an alkyl radical having from 1 to 5 carbon atoms, or a *cyclo*alkyl radical having from 3 to 7 carbon atoms;

A represents hydrogen or a β-alkoxy radical in which the alkyl moiety contains from 1 to 4 carbon atoms;

R' represents an alkyl radical having from 1 to 4 carbon atoms;

X_1 represents hydrogen, an alkyl radical containing from 1 to 4 carbon atoms, or the acyl residue of carbonic acid or carboxylic, aliphatic or alicyclic, organic acid having from 1 to 10 carbon atoms; and

Y_1 represents hydrogen, a methyl radical, an ethynyl radical, or a haloethynyl radical.

2. A composition as claimed in claim 1, wherein in the compound I the symbol R represents a methyl or ethyl radical.

3. A composition as claimed in either of the preceding claims, wherein in the compound I the symbol X represents: a hydrogen atom; an alkyl radical containing from 1 to 4 carbon atoms; an alkyl radical containing from 2 to 4 carbon atoms; an alkoxyalkyl radical containing from 2 to 4 carbon atoms; an unsaturated hydrocarbyl radical containing from 2 to 6 carbon atoms; the acyl residue of an alkanoic acid; the acyl residue of a *cyclo*alkylcarboxylic or *cyclo*alkylalkanoic acid; the acyl residue of benzoic acid; or the acyl residue of phenylacetic or phenylpropionic acid.

4. A composition as claimed in claim 3, wherein in the compound I the symbol X represents: a methyl, ethyl, propyl, *iso*propyl, butyl or *iso*butyl radical; a

methoxymethyl radical; a 2-methylallyl or 3-methyl-2-butenyl radical; the acyl residue of formic, acetic, propionic, butyric, *iso*butyric or undecylic acid; the acyl residue of *cyclo*propyl-, *cyclo*pentyl- or *cyclo*hexylcarboxylic acid, or *cyclo*propyl-, *cyclo*pentyl- or *cyclo*hexylacetic or -propionic acid.

5. A composition as claimed in any of the preceding claims, wherein in the compound I the symbol Y represents a hydrogen atom or a methyl radical.

6. A composition as claimed in any of the preceding claims, wherein in the compound II the symbol R_1 represents a hydrogen atom or a methyl radical.

7. A composition as claimed in any of the preceding claims, wherein in the compound II the symbol A represents a hydrogen atom or a methoxy radical.

8. A composition as claimed in any of the preceding claims, wherein in the compound II the symbol R' represents a methyl or ethyl radical.

9. A composition as claimed in any of the preceding claims, wherein in the compound II the symbol X_1 represents: a hydrogen atom; the acyl residue of formic, acetic, propionic, butyric or *iso*butyric acid; the acyl residue of *cyclo*propyl-, *cyclo*pentyl- or *cyclo*hexylcarboxylic acid; the acyl residue of *cyclo*propyl-, *cyclo*pentyl-, or *cyclo*hexylacetic or -propionic acid; the acyl residue of benzoic acid; or the acyl residue of phenylacetic or phenylpropionic acid.

10. A composition as claimed in any of the preceding claims, wherein in the compound II the symbol Y_1 represents a hydrogen atom or a methyl radical.

11. A composition as claimed in claim 1, wherein the anabolising steroid I is 2-oxa-13-β-ethyl-17α-methyl-17β-hydroxy-gona-4,9,11-trien-3-one.

12. A composition as claimed in either of claims 1 and 11, wherein the estrogenic steroid II is estradiol.

13. A composition as claimed in any of the preceding claims, wherein the compounds I and II are associated with a suitable vehicle.

14. A composition as claimed in claim 13, wherein the vehicle is:

a) the ingestible excipient of a tablet, coated tablet, or pill; the ingestible container of a capsule or catchet: the ingestible pulverulent solid carrier of a powder; or the ingestible liquid medium of a syrup, solution, suspension or elixir;

b) a sterile injectable liquid solution or suspension medium; or

c) a soluble material, or a base material, capable of releasing the active ingredient to perform its pharmacological function, which excipient material when appropriately shaped forms an implant.

15. A composition as claimed in any of the preceding claims, wherein there is, in a unit dose, from 1 mg to 300 mg of anabolising steroid I, and from 1 mg to 60 mg of estrogenic steroid II.

16. A composition as claimed in claim 15, wherein there is from 25 mg to 200 mg of compound I and from 10 mg to 50 mg of compound II.

17. A composition as claimed in any of the preceding claims and substantially as described hereinbefore.

18. A method for the zootechnical and/or veterinary treatment of a livestock animal, in which there is administered to the animal a composition as claimed in any of the preceding claims.

19. A method as claimed in claim 18, in which the composition is deposited as an implant in the dermis.

20. A method as claimed in either of claims 18 and 19 and substantially as described hereinbefore.

For the Applicants:
SANDERSON & CO.,
Chartered Patent Agents,
97, High Street,
Colchester, Essex.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1976.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.